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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/598,212	05/30/2008	Ann Margaret Dyer	10774-88US ARCCX/P32619US	1191

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EXAMINER	
BROWE, DAVID	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
08/13/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/598,212	DYER ET AL.	
	Examiner	Art Unit	
	DAVID M. BROWE	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-13 and 15-27* is/are pending in the application.

4a) Of the above claim(s) *24-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-13 and 15-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *January 4, 2010 and June 8, 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 6-13, and 15-23 are pending and under examination; claims 24-27 are withdrawn; claims 2-5, 14, and 28-35 are cancelled.

Applicants' timely submission of amendments and arguments in the reply filed June 8, 2010 in response to the First Office Action on the Merits is acknowledged.

Withdrawal of Prior Objection-Specification

The disclosure has been satisfactorily amended to comply with 37 CFR 1.77(b). Therefore, the objection presented in the First Office Action is hereby withdrawn.

Withdrawal of Prior Claim Rejections - 35 USC § 103

Neither Chenite *et al.* nor Dunn *et al.* explicitly discloses a preferred embodiment in which the composition is specifically for administration by the nasal or ocular routes and contains a therapeutic agent specifically for systemic action. Therefore, the 35 U.S.C. §103 rejection of claims 1-35 presented in the First Office Action is hereby withdrawn. However, a new prior art search has been conducted and a new grounds of rejection of the pending claims under examination has been formulated that addresses all pending limitations, and is presented herein below.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-13, and 15-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chenite *et al.* (U.S. Patent No. 6,344,488), in view of Dunn *et al.* (U.S. Patent No. 5,702,716) and Illum (U.S. Patent No. 5,629,011).

Applicant Claims

Applicants claim a composition in the form of an aqueous solution or suspension for nasal or ocular delivery of a therapeutic agent across a mucosal surface into

systemic circulation comprising: *a)* chitosan, a salt thereof, or a derivative thereof that has been formed by bonding of acyl or alkyl groups with the hydroxyl groups of the chitosan; *b)* a polyol-phosphate or sugar-phosphate salt; *c)* a plasticizer; and *d)* a therapeutic agent intended for systemic action. The chitosan, or derivative or salt thereof, has a molecular weight of 4,000 Da. or greater, particularly 50,000-300,000 Da; a degree of deacetylation of 40% or greater, particularly 70-90%; comprises from 0.25-3.0% to 0.45-1.5% w/v of the composition; and can be a chitosan base; or a nitrate, phosphate, sulphate, citrate, hydrochloride, glutamate, lactate, or acetate salt of chitosan. The polyol-phosphate or sugar-phosphate salt is β-glycerophosphate disodium; and comprises from 0.25-3.0% to 0.75-2.0% w/v of the composition. The plasticizer is triethyl citrate; and comprises from 0.05-5.0% to 0.2-1.0% w/v of the composition. The therapeutic agent is a polar drug, a polypeptide, a gene or a gene construct, insulin, calcitonin, leuprolide, luteinizing hormone releasing hormone, growth hormone or a growth hormone releasing factor, naratriptan, sumatripan, zolmitriptan, rizatriptan, eletriptan, frovatriptan, alnitidan, avitriptan, almotriptan, apomorphine, sildenafil, alprostadil, diamorphine, hydromorphine, buprenorphine, fentanyl, oxycodone, codeine, morphine, or morphine-6-glucuronide. The composition further comprises 0.01-0.2% w/v ascorbic acid.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Chenite *et al.* disclose a composition comprising: *a)* chitosan, or a derivative or salt thereof, *b)* a polyol-phosphate or sugar-phosphate salt, and *c)* a therapeutic agent (Col. 3, lns. 5-8, 14-25, 62-64; Col. 4, lns. 5-6, 30-31; Col. 5, lns. 65-66), and further

disclose that nasal and ophthalmic drug or peptide delivery can be effected by chitosan-based drug delivery systems (Col. 1, lns. 47-50; Col. 2, lns. 19-21; Col. 5, lns. 1-2). The composition is in the form of an aqueous solution or suspension at room temperature and upon ocular or body cavity administration (Col. 4, lns. 40-44; Col. 5, lns. 1-2; Col. 6, lns. 1-3; Col. 10, lns. 5-9; Col. 11, lns. 17-20, 28-31). The chitosan, or derivative or salt thereof, has a molecular weight of 4,000 Da. or greater, particularly 50,000-300,000 Da; comprises from 0.25-3.0% to 0.45-1.5% w/v of the composition; and can be a chitosan base or derivative formed by bonding of acyl or alkyl groups with the hydroxyl groups of the chitosan or a nitrate, phosphate, sulphate, citrate, hydrochloride, glutamate, lactate, or acetate salt of chitosan (Col. 3, lns. 16-17; Col. 4, lns. 45-46; Col. 7, lns. 7-10). The chitosan deacetylation degree and molecular weight employed, and the solution pH all greatly influence the solution properties, such as viscosity, as well as the gelation time at a particular temperature, and can be adjusted as desired through routine optimization (Col. 7, lns. 4-6, Col. 9, lns. 11-55; Col. 12, lns. 22-25, 29-33). The polyol-phosphate or sugar-phosphate salt is β-glycerophosphate disodium; and comprises from 0.25-3.0% to 0.75-2.0% w/v of the composition (Col. 3, lns. 18-21, 50-56). The therapeutic agent is a polar drug, a polypeptide, a gene or a gene construct, insulin, calcitonin, leuprolide, luteinizing hormone releasing hormone, growth hormone or a growth hormone releasing factor, naratriptan, sumatripan, zolmitriptan, rizatriptan, eletriptan, frovatriptan, alnitidan, avitriptan, almotriptan, apomorphine, sildenafil, alprostadil, diamorphine, hydromorphine, buprenorphine, fentanyl, oxycodone, codeine, morphine, or morphine-

6-glucuronide (Col. 13, lns. 9-22). The composition further comprises ascorbic acid (Col. 4, lns. 35-40)

Dunn *et al.* disclose a composition in the form of a solution or suspension for nasal or ocular delivery of a therapeutic agent across a mucosal surface into systemic circulation comprising: *a)* a thermoplastic polymer, *b)* a plasticizer, and *c)* a therapeutic agent intended for systemic circulation (Col 1, lns. 65-67; Col. 2, lns. 1-12, 15-30; Col. 3, lns. 35-43, 50-57; Col. 4, lns. 18, 31; Col. 8, lns. 19, 26, 31; Col. 10, lns. 1-47, 66; Col. 11, lns. 1-24). The thermoplastic polymer is chitosan; and has a molecular weight preferably between 15,000-100,000 Da (Col. 4, lns. 19, 31; Col. 5, lns. 59-61; Col. 6, lns. 43-56). The plasticizer is triethyl citrate; and comprises from 0.05-5.0% to 0.2-1.0% w/v of the composition (Col. 8, lns. 19, 26, 31, 43-53). The therapeutic agent is a polar drug, a polypeptide, a gene or a gene construct, insulin, calcitonin, leuprolide, luteinizing hormone releasing hormone, growth hormone or a growth hormone releasing factor, naratriptan, sumatripan, zolmitriptan, rizatriptan, eletriptan, frovatriptan, alnitidan, avitriptan, almotriptan, apomorphine, sildenafil, alprostadil, diamorphine, hydromorphine, buprenorphine, fentanyl, oxycodone, codeine, morphine, or morphine-6-glucuronide (Col. 10, lns. 1-67; Col. 11, lns. 1-24).

Illum discloses a composition in the form of an aqueous solution or suspension specifically for nasal delivery of a therapeutic agent across a mucosal surface into systemic circulation comprising: *a)* chitosan, a salt thereof, or a derivative thereof that has been formed by bonding of acyl or alkyl groups with the hydroxyl groups of the chitosan; and *b)* a therapeutic agent intended for systemic action (abstract; Col. 1, lns.

4-6, 60-67; Col. 2, lns. 58-61, 66-67; Col. 3, lns. 1, 14-28, 55-58; Col. 8, lns. 50-53). The chitosan, or derivative or salt thereof, has a molecular weight of 4,000 Da. or greater, particularly 50,000-300,000 Da; a degree of deacetylation of 40% or greater, particularly 70-90%; comprises from 0.25-3.0% to 0.45-1.5% w/v of the composition; and can be a chitosan base; or a nitrate, phosphate, sulphate, citrate, hydrochloride, glutamate, lactate, or acetate salt of chitosan (Col. 3, lns. 27-28, 55-58, 67; Col. 4, lns. 1-7; Col. 6, lns. 32-33). The therapeutic agent is a polar drug, a polypeptide, a gene or a gene construct, insulin, calcitonin, leuprolide, luteinizing hormone releasing hormone, growth hormone or a growth hormone releasing factor, naratriptan, sumatripan, zolmitriptan, rizatriptan, eletriptan, frovatriptan, alnitidan, avitriptan, almotriptan, apomorphine, sildenafil, alprostadil, diamorphine, hydromorphine, buprenorphine, fentanyl, oxycodone, codeine, morphine, or morphine-6-glucuronide (abstract; Col. 1, lns. 4-6, 60-67; Col. 8, lns. 65-67).

Ascertainment of the Difference Between the Scope of the Prior Art and the Claims (MPEP §2141.012)

Chenite *et al.*, however, do not explicitly disclose the incorporation of a plasticizer into the composition, and that the composition is specifically for administration by the nasal or ocular routes and contains a therapeutic agent specifically for systemic action. These deficiencies are cured by Dunn *et al.*, who teach that a chitosan-containing drug delivery composition can advantageously include a plasticizer, and by Illum, who teaches that a chitosan-containing drug delivery composition can advantageously be

administered by the nasal route and specifically mediate delivery of a therapeutic agent for systemic action.

Finding of Prima Facie Obviousness Rational and Motivation

(MPEP §2142-2143)

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the present invention to combine the respective teachings of Chenite *et al.*, Dunn *et al.*, and Illum, outlined *supra*, to arrive at applicants claimed composition. Chenite *et al.* disclose chitosan-based aqueous solutions containing active therapeutic agents that can be administered by any known means to an ophthalmic or other body cavity where they form sustained-release gels *in situ*. Since Dunn *et al.* disclose that triethyl citrate plasticizers can be incorporated in chitosan-based solutions containing active therapeutic agents for systemic delivery and action to provide significantly improved control of its sustained-release character by causing the formation of a heretofore unknown distinctive macromolecular structure (Col. 3, lns. 50-57; Col. 7, lns. 8-11, 16, 59-63), one of ordinary skill in the art would be motivated to employ a pharmaceutically acceptable plasticizer, such as triethyl citrate, in the composition of Chenite *et al.*, with the reasonable expectation that the plasticizer will successfully provide the means to fine-tune and significantly improve control of the desired therapeutic agent release rate of the composition *in situ*. Further, since Illum discloses that chitosan-based aqueous solutions containing active therapeutic agents that can be advantageously administered by the nasal route, and that the chitosan serves as an absorption promoting agent to facilitate trans-mucosal passage of the active therapeutic

agent from the gel into the systemic circulation, one of ordinary skill in the art would be motivated to incorporate active agents intended specifically for systemic action into the composition of Chenite *et al.*, and to administer the resulting composition specifically by the nasal route, with the reasonable expectation that the said composition will successfully provide sustained delivery of an effective amount of the active agent into the systemic circulation.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID M. BROWE whose telephone number is 571-270-1320. The examiner can normally be reached on Monday-Friday 7:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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